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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 2057.0090003/JAG/BJD

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

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Application Number	Filed
09/839,946	April 19, 2001

First Named Inventor: L. David WILLIAMS

Art Unit	Examiner
1652	Saidha, T.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 42,473

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Signature

Brian J. Del Buono
Typed or printed name

(202) 371-2600
Telephone number

Dec. 20, 2005
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5256
WILLIAMS *et al.*	Art Unit: 1652
Appl. No.: 09/839,946	Examiner: Saidha, T.
Filed: April 19, 2001	Atty. Docket: 2057.0090003/JAG/BJD
For: **PEG-Urate Oxidase Conjugates and Use Thereof**	

Arguments to Accompany the Pre-Appeal Brief Request for Review

Mail Stop AF

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby submit the following Arguments, in five (5) or less total pages, as attachment to the Pre-Appeal Brief Request for Review (Form PTO/SB/33). A Notice of Appeal is concurrently filed.

Arguments

Applicants' arguments in the Reply under 37 C.F.R. § 1.116 filed on October 20, 2005, in response to the final Office Action issued July 20, 2005, were not properly considered or responded to by the Examiner in the Advisory Action issued December 5, 2005. The Examiner's response was legally and factually deficient because the Examiner failed to show where the cited reference teaches an isolated tetrameric mammalian uricase, wherein at least about 90% of said uricase is in a tetrameric form and less than about 10% of said uricase is in a non-tetrameric aggregated form.

Under 35 U.S.C. § 102, a claim can be anticipated only if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984).

Claims 50-53 were rejected under 35 U.S.C. § 102(b) as anticipated by Lee *et al.*, *Science 239*: 1288-1291 (1988) (hereinafter "Lee"). The Examiner relied on Lee to teach an isolated tetrameric mammalian uricase, wherein at least about 90% of said uricase is in a tetrameric form and less than about 10% of said uricase is in a non-tetrameric aggregated form. Lee does not teach this limitation. Therefore, the Examiner's continued rejections based on 35 U.S.C. § 102(b) are legally and factually unfounded.

First, Lee does not *expressly* disclose the purification of *tetrameric* mammalian uricase as recited by the claims of the present application. Lee only indicates that porcine liver and murine urate oxidase were purified to homogeneity. Lee does *not* indicate that at least about 90% of the "purified" uricase was in a tetrameric form. Indeed, Lee does not indicate in *what* form the "purified" uricase was, let alone that at least about 90% of it was in a tetrameric form.

Second, while it is true that mammalian uricase ***in vivo*** exists as a tetramer, ***isolated*** preparations of natural and recombinant uricase, ***prior to the present invention***, contained a ***mixture*** of forms of the enzyme including non-tetrameric aggregates. *See* specification at page 16, lines 5-16. Therefore, prior to the present invention, it was not possible to isolate tetrameric uricase wherein at least about 90% of the uricase was in a tetrameric form. Indeed, using the methods disclosed in Lee, uricase present in a tetrameric form in the tissue, *i.e.*, *unisolated* uricase, would not remain in a tetrameric form upon being isolated from the tissue. Instead, the Lee methods would lead to rapid aggregation of the isolated uricase resulting in preparations in which less than about 90% was in a tetrameric form (and thus, in which more than about 10% was in a non-tetrameric aggregated form).

Contrary to the Examiner's continued contentions, the "homogeneous" uricase preparations of Lee are *not* tetramers -- they are monomers, formed from aggregates of isolated uricase by the SDS-PAGE process used in Lee. While the Examiner is correct that "in a denaturing gel such as SDS/PAGE, only the subunit form of the uricase is evident," Applicants respectfully contend that the commercial preparation (obtained from Sigma) of uricase analyzed by SDS-PAGE in Lee is not in the "native tetrameric form" as asserted by the Examiner. This

contention is supported by the present specification which discloses that a commercial preparation of uricase, also obtained from Sigma, had to be purified by the methods of the present invention in order to obtain the tetrameric form of uricase. *See* specification at page 20, lines 9-13. The specification further discloses that natural and recombinant uricases isolated from bacteria, fungi, mammals and plants require purification by the methods of the present invention in order to obtain isolated tetrameric uricases. *See* specification at Examples 4-10. In addition, as indicated above, prior to the present invention, uricase that is in the tetrameric form *in vivo* (*i.e.*, in an unisolated form) was known to rapidly form aggregates larger than tetramers upon being isolated from the tissue. Hence, if the isolated commercial preparation of uricase used by Lee was analyzed prior to bring denatured on SDS-PAGE, it would have been seen that that uricase preparation did *not* contain at least about 90% of the uricase in a tetrameric form and less than about 10% in a non-tetrameric aggregated form--most of it would instead have been in a non-tetrameric aggregated form. Therefore, the authors of Lee would not be expected to have produced a uricase preparation in which at least about 90% of the uricase was in a tetrameric form; instead, more than 10% of the uricase would have been present in a *non-tetrameric* aggregated form. This conclusion is further supported by the Declaration Under 37 C.F.R. § 1.132 by Merry R. Sherman, Ph.D., and the figures attached thereto, that was filed with Applicants' Amendment and Reply on May 26, 2005.

Given the discussion above, Lee clearly only discloses preparations of uricase in which more than about 10% of the uricase is either: (a) in a non-tetrameric aggregated form (*i.e.*, the commercial preparation); or (b) in a monomeric form after SDS-PAGE analysis. Lee, therefore, does *not* disclose preparations of isolated uricase in which at least about 90% is present in a tetrameric form. Indeed, Lee does not even expressly disclose purifying a tetrameric form of uricase, disclosing only the purification of uricase monomers. Thus, in disclosing "purification to homogeneity" of porcine and murine uricases, Lee is preparing uricase *monomers* and *not* uricase preparations in which at least about 90% of the uricase is tetrameric, as is presently claimed. That is, contrary to the Examiner's contentions, "homogeneity" in Lee does *not* mean

"greater than about 90% tetrameric" -- instead, "homogeneity" as used in Lee only means that the uricase has been purified away from non-uricase contaminants. This homogeneous uricase, however, could be present in *any* multimeric form or even in the monomeric form. Given that SDS-PAGE denatures multimeric proteins into their component monomeric forms, a preparation of uricase containing *any* multimeric form of the enzyme -- or even containing a *mixture* of multimeric forms which, as the present specification points out is the most likely form of the commercial uricase used by Lee -- would appear exclusively in the monomeric form after being run on an SDS-PAGE gel. Thus, this statement in Lee relating to homogeneity says nothing about the form, tetrameric or non-tetrameric, in which the uricase of Lee exists prior to SDS-PAGE analysis. Moreover, a homogenous preparation of isolated monomeric uricase -- which is the only isolated uricase expressly disclosed in Lee -- is not the same as an isolated tetrameric uricase which is recited by the present claims. Thus, as one of ordinary skill would readily appreciate, Lee does not disclose the production of mammalian uricases having the characteristics recited in the present claims.

While it is, of course, possible that the intermolecular association of four isolated monomers *in vitro*, under appropriate solution conditions, might theoretically make up an isolated tetrameric uricase, Lee neither expressly nor inherently discloses such preparations nor the appropriate solution conditions for producing such preparations from the monomeric subunits of uricase shown in the SDS-PAGE gels of this reference. As the Federal Circuit has held, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996). Accordingly, for at least these reasons, and under *Donohue* and *PPG Industries*, Lee cannot and does not anticipate the present claims.

Moreover, as indicated above, under 35 U.S.C. § 102, a claim can be anticipated only if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman* at 771. The Examiner has pointed to no express disclosure in Lee that would

support the Examiner's statement that the "homogeneous preparations of porcine or murine tetrameric uricase comprises the at least about 90% tetrameric form of mammalian uricase claimed." Advisory Action at page 3. Furthermore, the present specification clearly shows that by preparing uricases according to the methods of Lee, one of ordinary skill at best would only succeed in preparing uricases that contain *less* than about 90% tetrameric uricase. Thus, any reliance upon Lee in supporting an anticipation rejection is factually and legally unfounded.

Accordingly, Lee does not expressly or inherently disclose the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b). Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Lee therefore are respectfully requested.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

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